Remarks/Arguments

Claims 8-9 and 12-30 are canceled. Claims 1-3 and 10-11 are amended. New claims 31-33 are added. Support for the amendments and the new claims can be found, e.g., at page 25, line 10 – page 30, line 23 of the specification. No new matter is introduced.

Claims 1-7, 10-11, and 31-33 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

RESTRICTION REQUIRMENT

The Examiner made the Restriction Requirement final, while rejoining Groups II and V with elected Group I. Although Applicants do not concede the Examiner's position, for the sole purpose of moving this application forward, Applicants have amended claims 2-3 to exclude MITF and TRP-2 in claim 2 and the combinations including MITF or TRP-2 in claim 3.

CLAIM OBJECTIONS

The Examiner objected to claims 2 and 12 for being drawn to unelected inventions. As mentioned above, claim 2 has been amended to exclude MITF and TRP-2. Claim 12 has been canceled. The Examiner also objected to claim 10 for a typographical error. Applicants have corrected the error as suggested by the Examiner. The objections should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 112

(1) Claims 1-2 and 4-13 are rejected under § 112, 2nd paragraph as being indefinite. More specifically, the Examiner asserted that claims 1 and 12 are incomplete for omitting essential steps.

Although Applicants do not concede the Examiner's position, for the sole purpose of moving this application forward, Applicants have amended claim 1 to include a step of predicting melanoma recurrence, disease-free survival, overall survival, or a combination thereof, based on the levels of the nucleic acid targets. As such, claim 1 is complete. So are claims 2-7 and 10-11, dependant directly or indirectly from claim 1. Claims 8-9 and 12-13 have been canceled. The rejections should be withdrawn.

(2) Claims 1-2 and 4-13 are rejected under § 112, 1st paragraph for lack of enablement. More specifically, the Examiner asserted that the specification fails to teach a method involving isolating nucleic acid from any kind of biological sample or tissue and detecting the presence or absence of the nucleic acid targets (claims 1 and 12). The Examiner also asserted that the specification fails to teach a method involving differentiating between AJCC stages II-IV (claim 8), a method involving any prognosis (claim 9), or a method involving selecting any particular treatment regime (claim 11).

Although Applicants do not concede the Examiner's position, for the sole purpose of moving this application forward, Applicants have amended claim 1 to limit the biological sample to a sample associated with melanoma. It is well known in the art that SLN samples are only one kind of samples associated with melanoma. Other kinds of samples associated with melanoma include body fluid samples, non-SLN samples, and distant organ metastasis samples. One skilled in the art would understand that the SLN samples merely serve as examples in the present application, and that the method of claim 1 would apply to other samples associated with melanoma. Indeed, it has been demonstrated that the expression levels of a panel of marker genes including GalNAcT and PAX3 in blood samples obtained from melanoma patients are predictive of melanoma recurrence, disease-free survival, and overall survival. See, e.g., Koyanagi et al. (2005) J Clin Oncol

23(31):8057-64, the Abstract of which is attached hereto as "Exhibit A." In this connection, Applicants respectfully point out that "[t]he law does not require a specification to be a blueprint in order to satisfy the enablement requirement," and that one need not necessarily disclose how to make each and every embodiment encompassed by a claim. See, e.g., Staehlin v. Secher, 24 U.S.P.Q. 2d 1513, 1516 (Bd. Pat. App. & Int. 1992).

Applicants have also amended claim 1 to recite the levels of the nucleic acid targets. As shown at page 25, line 10 – page 30, line 23 of the specification, the levels of the nucleic acid targets are indicative of melanoma recurrence, disease-free survival, and overall survival.

Claims 8-9 and 12-13 have been canceled., rendering the Examiner's rejections moot.

As to claim 11, Applicants respectfully traverse the Examiner's rejection. It is well known and common practice in the art that treatment regimes can be selected based on the prognosis of cancer. For example, if a patient is predicted to remain disease-free after removal of a primary tumor and/or SLND, less management of the disease would be needed (see, e.g., page 13, lines 11-13 of the specification). On the other hand, if a patient is predicted to suffer from relapse after removal of a primary tumor and/or SLND, further lymph node removal surgery and/or adjuvant treatment would be needed (see, e.g., page 7, lines 14-16 of the specification).

In light of the forgoing, Applicants submit that claim 1, as amended, is fully enabled. Claims 2-7 and 10-11, dependant directly or indirectly from claim 1, also satisfy the enablement requirement. Withdrawal of the rejections is respectfully requested.

CLAIM REJECTIONS UNDER 35 USC § 102(b)

(1) Claims 1, 5, and 9-11 are rejected as being anticipated by Kuo et al. (Clinical Cancer Research 4:411-8; "Kuo").

Claim 1, as amended, is directed to a method for melanoma prognosis. The method comprises:

(a) isolating nucleic acid from a biological sample obtained from a melanoma patient, wherein the biological sample is associated with melanoma;

(b) amplifying nucleic acid targets from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3, or both;

(c) detecting the levels of the nucleic acid targets; and

(d) predicting melanoma recurrence, disease-free survival, overall survival, or a combination thereof, based on the levels of the nucleic acid targets.

Kuo, on the other hand, discloses detection of GalNacT in melanoma cell lines, as well as metastatic melanoma of lymph nodes and different organ sites (see, e.g., page 411, left column, Abstract, lines 16-19). There is no teaching whatsoever that the expression of GalNacT can be used to predict melanoma recurrence, disease-free survival, or overall survival. Therefore, Kuo does not anticipate claim 1, because it fails to teach every limitation of claim 1. Claims 5 and 10-11, dependant from claim 1, are not anticipated by Kuo for at least the same reason. Claim 9 has been canceled. Applicants respectfully request that the rejections be withdrawn.

(2) Claims 1-2 are rejected as being anticipated by Scholl et al. (Cancer Research 61:823-6; "Scholl").

As mentioned above, claim 1, as amended, is directed to a method for melanoma prognosis. The method comprises a step of predicting melanoma recurrence, disease-free survival, or overall survival based on the expression levels of a panel of marker genes including PAX3.

Scholl, on the other hand, discloses detection of PAX3 in melanoma cell lines, as well as cultured primary melanomas and their corresponding tissue sections (see, e.g., page 823, left column, Abstract, lines 5-11 and right column, last two paragraphs). There is no teaching whatsoever that the expression of PAX3 can be used to predict melanoma recurrence, disease-free survival, or overall survival. Therefore, Scholl does not anticipate claim 1, because it fails to teach every limitation of claim 1. Claim 2, dependant from claim 1, is not anticipated by Scholl for at least the same reason. Applicants respectfully request that the rejections be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 103(a)

Claims 1-2 and 4-13 are rejected as being unpatentable over Palmieri et al. (Journal of Clinical Oncology 19(5):1437-43; "Palmieri") in view of Kuo, Scholl, and Danenberg et al. (U.S. Patent Application Publication No. 2001/0029018 A1; "Danenberg").

As mentioned above, claim 1, as amended, is directed to a method for melanoma prognosis. The method comprises a step of predicting melanoma recurrence, disease-free survival, or overall survival based on the expression levels of a panel of marker genes including GalNAcT, PAX3, or both.

Palmieri, the primary prior art reference cited by the Examiner, discloses detection of a combination of Tyrosinase and MART-1 in SLN and peripheral-blood (PB) samples obtained from melanoma patients and its prognostic significance (see, e.g., page 1437, left column, 1st paragraph, lines 7-13). However, Palmieri fails to teach or suggest that the expression levels of a panel of marker genes including GalNAcT, PAX3, or both, can be used to predict melanoma recurrence, disease-free survival, or overall survival.

As mentioned above, there is no teaching or suggestion whatsoever in Kuo or Scholl that the expression of GalNacT or PAX3 can be used to predict melanoma recurrence, disease-free survival, or overall survival. Therefore, neither Kuo nor Scholl can cure the defect of Palmieri.

Danenberg discloses quantitative measurement of gene expression based on isolation of RNA from formalin-fixed paraffin-embedded tissue specimens (see, e.g., Abstract). Like Kuo and Scholl, there is no teaching or suggestion whatsoever in Danenberg that the expression of GalNacT or PAX3 can be used to predict melanoma recurrence, disease-free survival, or overall survival. Therefore, Danenberg cannot cure the defect of Palmieri, either.

It is the discovery of the present invention that the expression levels of a panel of marker genes including GalNAcT or PAX3 are indicative of melanoma recurrence, disease-free survival, or overall survival (see, e.g., page 25, line 10 – page 30, line 23 of the specification). Without such knowledge, one skilled in the art would not have been motivated to combine Palmieri, Kuo, Scholl, and Danererg to come up with the method of claim 1. Thus, claim 1 is patentable over the cited art. Claims 2-7 and 10-11, dependant directly or indirectly from claim 1, are also patentable over the cited art for at least the same reason. Claims 8-9 and 12-13 have been canceled. The rejections should be withdrawn.

NEW CLAIMS 31-33

New claim 31 is directed to a method for detecting the expression of a panel of marker genes in a patient. The method comprises:

(a) obtaining an SLN sample from a melanoma patient, wherein the sample is histopathologically negative for melanoma cells;

(b) isolating nucleic acid from the sample;

(c) amplifying nucleic acid targets from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3, or both; and

(d) detecting the levels of the nucleic acid targets.

Claim 31 is novel over the cited art, because neither Kuo nor Scholl discloses detection of GalNAcT or PAX3 in an SLN sample from a melanoma patient, wherein the sample is histopathologically negative for melanoma cells. In particular, in Kuo, tumor-draining lymph node (TDLN) metastases were used for GalNAcT detection (see, e.g., page 414, Table 2). All TDLN specimens were verified by hematoxylin and eosin (H&E) or immunohistochemistry as positive for metastatic melanoma (see, e.g., page 413, right column, 1st paragraph under Table 1, lines 14-15). In Scholl, cultured primary melanomas and their corresponding tissue sections were used for PAX3 detection (see, e.g., page 823, left column, Abstract, lines 7-11 and right column, last paragraph, lines 4-6). Claim 31 is also non-obvious over the cited art for at least a reason similar to that presented above. Further, both Kuo and Scholl teach away from claim 31 by selecting TDLN metastases for GalNAcT detection and primary melanomas for PAX3 detection, respectively. New claims 32-33, dependant directly or indirectly from claim 31, are novel and non-obvious over the cited art for at least the same reasons.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
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Date: June 26, 2006

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1: J Clin Oncol. 2005 Nov 1;23(31):8057-64.

Related Articles, Links

Full text article at www.jco.org

Serial monitoring of circulating melanoma cells during neoadjuvant biochemotherapy for stage III melanoma: outcome prediction in a multicenter trial.

Koyanagi K, O'Day SJ, Gonzalez R, Lewis K, Robinson WA, Amatruda TT, Wang HJ, Elashoff RM, Takeuchi H, Umetani N, Hoon DS.

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PURPOSE: Circulating tumor cells (CTCs) in blood may be important in assessing tumor progression and treatment response. We hypothesized that quantitative real-time reverse transcriptase polymerase chain reaction using multimarker mRNA assays could detect CTCs and be used as a surrogate predictor of outcome in patients receiving neoadjuvant biochemotherapy (BC) for melanoma. PATIENTS AND METHODS: Blood specimens were collected at four sampling points from 63 patients enrolled on a prospective multicenter phase II trial of BC before and after surgical treatment of American Joint Committee on Cancer stage III melanoma. Each specimen was assessed by quantitative real-time reverse transcriptase polymerase chain reaction for expression of four melanoma-associated markers: melanoma antigen recognized by T cells 1; beta1 --> 4-N-acetylgalactosaminyltransferase; paired box homeotic gene transcription factor 3; and melanoma antigen gene-A3 family, and the changes of CTCs during treatment and prognostic effect of CTCs after overall treatment on recurrence and survival were investigated. RESULTS: At a median postoperative follow-up time of 30.4 months, 44 (70%) patients were clinically disease free. In relapse-free patients, the number of detected markers significantly decreased during preoperative BC ($P = .036$), during postoperative BC ($P = .002$), and during overall treatment ($P < .0001$). Marker detection after overall treatment was associated with significant decreases in relapse-free and overall survival ($P < .0001$). By multivariate analysis using a Cox proportional-hazards model, the number of markers detected after overall treatment was a significant independent prognostic factor for overall survival (risk ratio, 12.6; 95% CI, 3.16 to 50.5; $P = .0003$). CONCLUSION: Serial monitoring of CTCs in blood may be useful for

indicating systemic subclinical disease and predicting outcome of patients receiving neoadjuvant BC for metastatic melanoma.

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- Multicenter Study

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